Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

patients requiring anti-TNF therapy during the pandemic may preferentially be started on the least immunogenic agent (in our practice, adalimumab over infliximab), and this emerges as an important focal point for further research.

The data presented in the manuscript implicating sulfasalazine/5-aminosalicylate (5-ASA) therapy with poor outcomes are worrying, counterintuitive, and surprising based on the lack of immune-modulatory activity. Many possible explanations require exploration. We propose that the observed association with 5-ASA may partly be a surrogate marker for underlying IBD activity, and note that the record of disease activity in the registry, for pragmatic reasons, is based on a physician global assessment. We observe the elevated (12%) intensive care unit/ventilator/death rate in those patients with reported moderate to severely active IBD, and that other studies have also reported a detrimental association between all IBD activity and COVID-19 outcomes.[6] Similarly, it is possible that the more serious COVID-19 outcomes in patients on steroids may at least be partly confounded by an association with active IBD. Recent data have implicated active colitis as associated with increased colonic expression of the angiotensin-converting enzyme 2 epithelial cellular receptor for SARS-Cov-2,[7] providing a possible mechanistic link. Of note neither 5-ASA nor steroids are reported to independently alter intestinal mucosal angiotensin-converting enzyme 2 expression.[8]

Overall, we congratulate the authors for their timely establishment of a critically important resource during the pandemic, and for addressing important issues. We point to the need for further data to substantiate these initial observations, and for detailed case-control and cohort-based studies to address the key issues in patient management. As data accrue, evidence-based alterations to current clinical guidelines will be of additional benefit to our patients, not only in relation to therapy decisions, but also to social distancing guidelines and their ability to safely perform their roles within society. At present these, and other, published data suggest that in the COVID-19 era, we should closely monitor for objective IBD activity so as not to delay effective management, using where possible biologic monotherapy and avoiding systemic steroids. Importantly, we feel these data should not negatively affect the appropriate use of 5-ASA in management algorithms.

OLIVER BRAIN
JACK SATSANGI
Gastroenterology Unit
John Radcliffe Hospital
Oxford, United Kingdom

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Conflicts of Interest
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Most current article

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Aminosalicylates and COVID-19: Facts or Coincidences?

Dear Editors:

It was with great interest that we read the paper of Brenner et al[1] published recently in *Gastroenterology*. In the setting of Coronavirus Disease 2019 (COVID-19), the authors defined severity as the need for intensive care unit admission and ventilator use, and/or death. The paper reports that tumor necrosis factor (TNF) antagonists do not appear to be associated with severe COVID-19, but sulfasalazine or 5-aminosalicylate (5-ASA) use adjusted for age, comorbidities, inflammatory bowel disease (IBD) disease characteristics, and corticosteroids were positively associated with the outcome of hospitalization or death (adjusted odds ratio 3.1; 95% CI, 1.3–7.7).[1] These findings are surprising and unexpected, because neither immunomodulators nor TNF antagonists have been associated positively with the composite outcome. Oral delayed-release mesalamine is a pH-dependent drug; the formulation allows delayed release from the terminal ileum to the colon, resulting in local topical activity on the mucosa and low systemic concentration.[2] Depending on the dose and type of formulation, only 15% to 67% of the drug is absorbed and excreted in the urine (mostly in the acetylated form), whereas 24% to 67% passes to the stool (approximately 50% in acetylated form). Colonic epithelial cells acetylate 5-ASA rapidly, however N-acetyl 5-ASA is poorly absorbed by epithelial cells.[3] Therefore, how can we explain that aminosalicylates with low bioavailability are associated with poor outcomes in patients with IBD with COVID-19? Two explanations occur: one relates to methodological aspects, and the other with mechanistic pathways of 5-ASA. To guarantee that we are following the right path, we suggest a complementary analysis to the work of Brenner et al.[1]:

1. In the multivariate regression, the group of 5-ASA should analyze patients on monotherapy with aminosalicylates (without other concomitant drugs to treat IBD).
2. Comorbidities like hypertension, diabetes, and cardiovascular conditions were reported to be associated with worst prognosis in patients with COVID-19, and to have different weight from that of history of stroke, asthma, NAFLD, or cirrhosis. In this work, the authors considered all comorbidities as having similar influence. From our point of view, this can be a potential

source of bias, particularly because 10% of the comorbidities were classified as "Others."

3. Including more than 1 covariate per 10 events, in the regression model, may lead to bias.[4]

After setting these aspects, the other hypothesis may be related to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor, on a mechanistic perspective. A less explored mechanism of action of 5-ASA is its capacity to bind the peroxisome proliferator-activated receptor gamma (PPAR-γ).[5] PPAR-γ is highly expressed in adipocytes but also in the colon.[6] The binding of 5-ASA to PPARγ has clinical relevance because it occurs for concentrations that are effective in maintenance therapy in patients with IBD.[5] Besides, 5-ASA induces the expression of PPAR-γ.[5,7] The expression of PPAR-γ is lower in the intestinal epithelium of patients with ulcerative colitis when compared to controls or patients with Crohn's disease, and correlates with ulcerative colitis activity.[7] In adipocytes and in the vascular tissue, PPAR-γ also increases the expression of the angiotensin-converting enzyme 2 (ACE2),[5,7] the binding receptor for SARS-CoV-2. However, COVID-19 severity is partly influenced by the mechanism responsible for viral entry in the host cell. It is important to note that ACE2 might be internalized with the virus, or be kept in the host cell membrane, or shed to the circulation. Only shed or membrane-bound ACE2 can act as a protective enzyme of the renin-angiotensin system, with favorable outcomes. Also, PPAR-γ activation inhibits the expression of TMPRSS2, a transmembrane serine protease relevant for both viral entry with ACE2 internalization.[8]

In conclusion, studies that explore the nature of the puzzle among 5-ASA, PPARγ, and ACE2 are imperative to ascertain whether 5-ASA determines more severe outcomes in patients with IBD with COVID-19: fact or coincidence?

FERNANDO MAGRO
Department of Gastroenterology
São João Hospital Center
Department of Biomedicine
Unit of Pharmacology and Therapeutics, Faculty of Medicine
University of Porto
Department of Clinical Pharmacology
São João Hospital University Center
Porto, Portugal

CLAUDIA CAMILA DIAS
Centre for Health Technology and Services Research (CINTESIS)
Department of Community Medicine
Information and Health Decision Sciences
Faculty of Medicine, University of Porto
Porto, Portugal

MANUELA MORATO
LAQV@REQUIMTE
Laboratory of Pharmacology
Department of Drug Sciences
Faculty of Pharmacy, University of Porto
Porto, Portugal

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Most current article

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The Course of COVID-19 in Inflammatory Bowel Disease: Protective Role of TNF Antagonists

Dear Editors:

We have read with great interest the paper by Brenner et al,[1] which reports the preliminary results of an international registry of patients with inflammatory bowel disease (IBD) and severe acute respiratory syndrome coronavirus 2 infection: the Surveillance Epidemiology of Coronavirus Under Research Exclusion (SECURE-IBD). We acknowledge that data collection is still ongoing and that the sample size has significantly increased, with 1170 patients included at the time of this writing.[2] However, we think the results deserve a few considerations: the rate of patients on anti–tumor necrosis factor (anti-TNF), either in monotherapy or in combination, is higher than expected, being 43.4% of the studied population. Based on current clinical guidelines and the heterogeneity of the 33 participating centers, we would have expected a rate of patients on anti-TNFs not exceeding 30%, even in the United States.[3] Possibly, patients on conventional maintenance therapy with mesalamine with severe acute respiratory syndrome coronavirus 2 infection but with asymptomatic or mild clinical course have never been tested for Coronavirus Disease 2019 (COVID-19) either by nasopharyngeal swab or serological tests and subsequently have never been diagnosed. On the other hand, patients on biologics undergo a closer follow-up and are intensively tested because of the immunosuppression status. Because of selection bias, the negative role of mesalamine should be furtherly explored. The protective role of anti-TNF is convincing based on the available, although still not yet fully proven, evidence on the efficacy of biologics in the cytokine storm phases of COVID-19 infection, where at the